Journal Club

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Emerging Role of Astrocytes in Striatal Synaptic Plasticity

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Review of Cavaccini et al.

It is increasingly clear that astrocytes are active participants in many brain functions. They detect neuronal activity with various surface receptors they express. Activation of astrocytic receptors leads to Ca^{2+} and other second-messenger signaling, which in turn triggers the release of so-called gliotransmitters. These gliotransmitters can regulate synaptic transmission and plasticity, providing feedback or feed-forward modulation of neuronal circuitry (Araque et al., 2014). Early studies on astrocyte–neuron interaction, however, were mainly focused on the hippocampus. Our understanding of astrocyte–neuron communication in other brain regions is at a nascent stage.

One region of particular interest to those who study action selection and movement control is the striatum, which is the major input nucleus of the basal ganglia (Graybiel and Grafton, 2015). As testimony to its importance, the striatum is implicated in many neurological and psychiatric diseases such as Parkinson's disease and obsessive-compulsive disorder. The principal neurons of the striatum are spiny projection neurons (SPNs; Zhai et al., 2018). SPNs can be divided into two populations, direct pathway SPNs (dSPNs) and indirect pathway SPNs (iSPNs), which contrast each other in anatomic properties,

receptor compositions, and circuit functions. Balanced and coordinated activities of dSPNs and iSPNs are key to appropriate movement initiation and smooth execution of action sequences (Klaus et al., 2019). Synaptic plasticity at corticostriatal glutamatergic synapses has long been considered the cellular underpinning of goal-directed and habitual learning (Yin and Knowlton, 2006). Among the various forms of plasticity reported, high-frequency stimulation (HFS)-induced long-term synaptic depression (LTD) is most extensively studied. For iSPNs, the underlying mechanism is quite clear and involves postsynaptic synthesis of endocannabinoids and retrograde activation of presynaptic CB1 receptors (Surmeier et al., 2007). For dSPNs, however, there is less consensus. While an early study failed to induce HFS-LTD in dSPNs (Kreitzer and Malenka, 2007), a more recent study, with a few differences in experimental conditions, showed that HFS-LTD could be induced in dSPNs through adenosine signaling (Trusel et al., 2015). As a source of adenosine (Araque et al., 2014), could astrocytes mediate this form of long-term synaptic plasticity? In a recent article, Cavaccini et al. (2020) provided evidence, for the first time, that astrocytes are an active participant of synaptic plasticity in the striatum.

As their first step, Cavaccini et al. (2020) investigated the molecular mechanism of HFS-LTD in dSPNs using pharmacological approaches. They performed whole-cell patch-clamp recordings from SPNs in the dorsolateral striatum while applying electrical stimulation to the co-

rtex in horizontal slices. Recorded cells were identified by *post hoc* immunostaining for A2a receptors (for iSPNs) and substance P (for dSPNs). Confirming their previous finding (Trusel et al., 2015), the authors showed that an HFS-LTD protocol (1 s 100 Hz HFS paired with 1 s postsynaptic depolarization from -80 to -50 mV, repeated four times with an interval of 10 s) induced a persistent decrease in EPSP or EPSC amplitude in dSPNs. The synaptic depression was accompanied by a decrease in the inverse squared coefficient of variation (CV^{-2}), implying that this LTD was caused by a reduction in presynaptic glutamate release. The authors also demonstrated that HFS-LTD in dSPNs was prevented by the application of an adenosine A1 receptor (A1R) antagonist but not by antagonism of CB1 receptor, in stark contrast to HFS-LTD in iSPNs (Kreitzer and Malenka, 2007). Further revealing the underlying mechanism, the authors showed that this A1R-dependent LTD in dSPNs also required metabotropic glutamate receptor type 5 (mGluR5), but not GABA_A or GABA_B receptors.

Cavaccini et al. (2020) then addressed the pressing question: what is the source of the adenosine responsible for LTD induction? As astrocytes release adenosine and thereby modulate synaptic transmission in other brain regions (Araque et al., 2014), the authors hypothesized that striatal astrocytes are the source of the adenosine necessary for HFS-LTD induction in dSPNs. To test this exciting idea, they first determined whether striatal astrocytes were activated by cortical HFS. To monitor the activity of astrocytes, they virally

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expressed genetically encoded Ca^{2+} indicator GCaMP6f in striatal astrocytes. With two-photon imaging of *ex vivo* slices, they found that astrocyte Ca^{2+} activity was elevated during and immediately after HFS but returned to baseline within 12 min. Furthermore, they showed that this HFS-evoked elevation in astrocyte Ca^{2+} activity was prevented by an mGluR5 antagonist, mirroring the dependence of HFS-LTD on mGluR5. Together, their data suggest that glutamate released by HFS activates the mGluR5 on striatal astrocytes, which in turn leads to the mobilization of intracellular Ca^{2+} in astrocytes. One caveat the authors do not address is that the observed astrocyte Ca^{2+} elevation was caused by HFS alone, not the HFS-LTD protocol that involves depolarization of postsynaptic neurons. Postsynaptic depolarization, in synergy with HFS, may lead to dendritic release of signaling molecules that directly or indirectly modulate astrocyte signaling (Nagai et al., 2019).

Next, Cavaccini et al. (2020) determined whether an elevation in astrocyte Ca^{2+} activity was required for HFS-LTD in dSPNs. To block the elevation in astrocyte Ca^{2+} activity, the authors took advantage of a genetic tool—IP₃R2 knock-out mice in which astrocytes lack IP₃R-mediated Ca^{2+} events—and a pharmacological tool, GDP β S [guanosine-5'-(β -thio)-diphosphate], which was patch loaded into the astrocyte network to inhibit astrocytic GPCR signaling. As they expected, both measures significantly suppressed HFS-evoked elevation in astrocyte Ca^{2+} activity. More importantly, they found that both measures effectively prevented HFS-LTD. Their data strongly suggest that the activation of GPCRs on astrocytes and the subsequent astrocyte Ca^{2+} activity are required for HFS-LTD induction.

Having demonstrated the necessity of astrocytes in dSPN LTD, Cavaccini et al. (2020) then asked whether astrocyte activation was sufficient to induce A1R-dependent LTD in dSPNs. To address this question, the authors adopted a chemogenetic approach and virally expressed a G_q -coupled DREADD (designer receptor exclusively activated by designer drugs) in astrocytes. Their rationale was that activation of the G_q -DREADD by clozapine N-oxide (CNO) should mimic the activation of astrocytic mGluR5, causing Ca^{2+} rise and subsequent ATP/adenosine release. As they expected, CNO led to a strong rise in Ca^{2+} signal in DREADD-expressing

astrocytes. More importantly, CNO application for 30 min led to a significant decrease of EPSC amplitude in dSPNs. This decrease was blocked by an A1R antagonist, which also unmasked synaptic potentiation that was sensitive to group I mGluR antagonists. Collectively, these data strongly argue that the activation of astrocytes decreases the synaptic response of dSPNs through A1R receptors.

Unexpectedly and interestingly, Cavaccini et al. (2020) found that the CNO-induced LTD did not occlude HFS-LTD in dSPNs. In the Discussion, Cavaccini et al. (2020) mentioned the following two possible scenarios: (1) the pre-synaptic mechanism was not saturated by CNO-induced LTD; and (2) CNO activation of DREADD-expressing astrocytes might trigger different mechanisms. The latter possibility was repeatedly hinted at by their results. First, CNO-induced LTD and HFS-LTD seem to have different time courses. Although CNO evoked an immediate astrocyte Ca^{2+} signal, a 30 min perfusion of CNO was used to achieve discernible synaptic depression. In contrast, synaptic depression was manifested immediately after the HFS-LTD protocol (Trusel et al., 2015). Second, CNO-induced LTD lacks both the post-synaptic and network signaling events that may occur in HFS-LTD. In addition to postsynaptic depolarization (discussed above), the HFS-LTD protocol inevitably engages network modulation (Surmeier et al., 2007), for example by dopamine and acetylcholine, for which astrocytes express abundant receptors (Haydon and Nedergaard, 2014). Finally, CNO-induced LTD was not accompanied by any significant decrease in CV^{-2} , suggesting that the activation of G_q -DREADD on astrocytes reduces synaptic response without altering presynaptic glutamate release. Indeed, in addition to presynaptic terminals, postsynaptic dSPNs also express A1R (Ferre, 2008). Being $G_{i/o}$ coupled, A1Rs may work in the opposite direction of D_1 dopamine receptors: inhibiting LTP, promoting LTD, and suppressing intrinsic excitability (Surmeier et al., 2007). Because the authors used a potassium-based pipette solution, the observed decrease in synaptic responses following astrocyte activation could be caused by reduced synaptic transmission, dampened somatodendritic excitability, or a combination of both. The interesting results of the study by Cavaccini et al. (2020)

highlight the heterogeneity and complexity of astrocyte modulation of neuronal network activity.

Although focused on one form of synaptic plasticity in dSPNs, the work by Cavaccini et al. (2020) inspires us to ponder our current models of striatal synaptic plasticity. Do astrocytes play a role in other forms of synaptic plasticity? It seems very possible, but probably in a cell type-specific way. It has been shown that dSPNs and iSPNs are associated with different astrocyte subpopulations (Martin et al., 2015). Astrocyte subpopulations may be equipped with different molecular machineries, such as GPCRs and gliotransmitters, that allow differential modulation of neuronal networks. Hence, astrocytes might play an integral but specific role in various forms of striatal synaptic plasticity.

Further, do striatal astrocytes shape circuit activity and behavior? The work by Cavaccini et al. (2020) reveals a mechanism by which astrocytes selectively suppress dSPNs. On the other hand, through activating $G_{s/o}$ -linked A2a adenosine receptors, astrocyte-released adenosine may selectively excite iSPNs (Higley and Sabatini, 2010; Peterson et al., 2012). Hence, astrocytes are well situated to bidirectionally regulate direct and indirect pathways and thereby control behavior. Corroborating this idea, a recent study showed that the activation of astrocytes in the dorsomedial striatum, by the same chemogenetic tool used by Cavaccini et al. (2020), differentially regulated synaptic transmission in dSPNs and iSPNs and facilitated shifting from habitual to goal-directed reward-seeking behavior (Kang et al., 2020).

In conclusion, the work by Cavaccini et al. (2020) provides strong evidence for an integral role of astrocytes in HFS-LTD in dSPNs. In doing so, this work underscores the need for future studies to elucidate the role of astrocytes in synaptic and intrinsic plasticity in the striatum. It also paves the way for understanding how astrocytes regulate normal behavior and how dysfunctional astrocytes contribute to pathological behaviors and movement disorders.

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